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ORIGINAL REPORT

Insulin Resistance and Risk Factors for Cardiovascular Disease in Young Adult Survivors of Childhood Acute Lymphoblastic Leukemia

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ABSTRACT

Purpose
To determine the prevalence of insulin resistance and other risk factors for cardiovascular disease (CVD) in young adult survivors of childhood acute lymphoblastic leukemia (ALL).

Patients and Methods
In this cross-sectional evaluation of 118 survivors of childhood ALL (median age, 23.0 years; range, 18 to 37 years), insulin resistance was estimated using the homeostasis model for assessment of insulin resistance (HOMA-IR). Sex-specific comparisons were made with a cohort of 30- to 37-year-old individuals from the same region participating in the Dallas Heart Study (DHS, N = 782). ALL survivors were stratified by treatment with and without cranial radiotherapy (CRT).

Results
Female ALL survivors had a significantly higher HOMA-IR (CRT, mean 4.6, 95% CI, 3.6 to 5.7; no CRT, mean 3.3, 95% CI, 2.8 to 3.8) in comparison with DHS women (mean 2.4, 95% CI, 2.2 to 2.7). Eighty percent of women treated with CRT had at least three of six CVD risk factors, and they were significantly more likely to have three or more risk factors compared with DHS women (odds ratio [OR], 5.96; 95% CI, 2.15 to 16.47). Male ALL survivors had a significantly higher HOMA-IR (CRT, mean 4.0, 95% CI, 2.8 to 5.6; no CRT, mean 3.4, 95% CI, 2.9 to 3.9) in comparison with DHS men (mean 2.3, 95% CI, 2.1 to 2.6), but were not more likely to have multiple CVD risk factors.

Conclusion
ALL survivors had an increased prevalence of insulin resistance in comparison with a cohort of older individuals from the same community. Importantly, women treated with CRT seem to have an increased prevalence of multiple CVD risk factors, warranting close monitoring and risk-reducing strategies.

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INTRODUCTION

Long-term survivors of childhood acute lymphoblastic leukemia (ALL) have a significantly elevated risk of premature mortality and serious morbidity.[1-4] Among 3,061 leukemia survivors, at a median age of 26 years, the likelihood of having a severe or life-threatening chronic condition was more than four times as high as that of siblings of childhood cancer survivors.[5] Reflecting the relatively recent increase in long-term survival rates, these estimates were based on relatively young ALL survivors, with few over the age of forty. With more than 80% of children with ALL now becoming long-term survivors,[6] the number who are middle-aged will increase over the next 10 to 20 years.

Recent studies suggest that ALL survivors have an increased prevalence of obesity[7,8] and physical inactivity[9,10] and may be at risk of developing diabetes, dyslipidemia, and metabolic syndrome.[11-15] Importantly, each of these factors may contribute to the development of cardiovascular disease and is potentially preventable. Thus it is imperative to further study this population, determine whether their risk of cardiovascular disease is increased, and develop interventions aimed at decreasing risk.

The two-phase ALLIFE study was designed to further assess cardiovascular risk in a population of young adult survivors of childhood ALL and to test the effectiveness of a 12-month lifestyle intervention in increasing levels of physical activity and improving cardiorespiratory fitness. This article reports results from the first phase of the ALLIFE study. Our

primary aim was to determine the prevalence of insulin resistance and other risk factors for cardiovascular disease (CVD) in this cohort. We compared these cancer survivors to a noncancer population of men and women living in the same geographic region.

PATIENTS AND METHODS

Study Population: ALLIFE Participants

As previously described, the ALLIFE study, conducted from May 2004 to January 2007, consists of a cohort of 118 young adult survivors of childhood ALL diagnosed between 1970 and 2000 and who live in the Dallas area.[16] Of 189 eligible survivors, 16.4% and 21.2% actively and passively refused to participate, respectively. The remaining 118 eligible participants enrolled onto the study (62.4%). Key demographic characteristics, including sex, age, race/ethnicity, age at cancer diagnosis, and interval from cancer to present time, were not significantly different ($P > .1$) between eligible survivors who did not enroll onto the study and participants.

The median age of participants at the time of study was 23.0 years (range, 18 to 37 years). The median interval from cancer diagnosis to study enrollment was 17.5 years (range, 5 to 34 years). Fifty-six percent were women, and 27.1% were members of an ethnic or racial minority group.

Participants were treated on one of several protocols: 38.1% were treated on the DFW-1 protocol; 39.0% were treated on a Pediatric Oncology Group protocol, including POG 8036, 9201/2/3, and 9404; 4.2% were treated on a Children's Cancer Group protocol; and 18.7% were treated on an institutional or miscellaneous protocol. Thirty-four percent of the participants were treated with cranial radiotherapy (CRT; < 24 Gy, 9.3%; ≥ 24 Gy, 24.6%); 74% were treated with an anthracycline (< 300 mg/m^2, 54.4%; ≥ 300 mg/m^2, 19.3%). Other key treatment exposures included dexamethasone (11.4%), cyclophosphamide (43.0%), and etoposide (34.2%). More than 95% of the cohort was treated with vincristine, methotrexate, and/or prednisone.

All study participants provided written informed consent for study participation and release of medical record information. The study was approved by the institutional review boards at The University of Texas Southwestern Medical Center and The Cooper Institute.

Comparison Population: Dallas Heart Study

For comparison, we used an older cohort of individuals without cancer who live in the same region. The Dallas Heart Study (DHS) is a probability-based cohort that consists of 6,101 Dallas County residents, with an oversampling of racial and ethnic minorities.[17] To account for oversampling, sampling weights were calculated for each participant according to the subject's initial selection probability, which depended on race and ethnicity, sex, and age stratum. Of this cohort, 2,971 participants between the ages of 30 and 65 years underwent specialized testing between July 2000 and October 2002. Because the age of the ALLIFE participants ranged from 18 to 37 years, the 782 DHS participants who were 30 to 37 years of age were used as a comparison group.

The prevalence of insulin resistance and other CVD risk factors increases with advancing age, particularly during late adolescence and young adulthood.[18-21] These outcomes also vary across geographic regions.[22,23] Recognizing that ALLIFE participants were an average of 10 years younger than those in the DHS comparison group, we felt that it was important to have a comparison population obtained from the same geographic region using similar measurement methodologies.

Outcome Measurements

Anthropometric and radiographic measures of body composition. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured at the level of superior iliac crest to the nearest 0.1 cm. In the ALLIFE study, body composition was measured by dual energy x-ray absorptiometry (DXA) using a Lunar DPX scanner (MEC, Minster, OH). A Delphi W scanner (Hologic Inc, Bedford, MA) was used in the DHS.

Blood pressure measurement. Blood pressure was measured in both studies using an automatic oscillometric device (Series No. 52,000, Welch Allyn, Inc, Arden, NC).[24]

Laboratory analysis. In both studies, participants had venous blood samples obtained after a 12-hour overnight fast, as previously described.[15,17,25,26] Glucose was measured through The University of Texas Southwestern Medical Center GCRC Core Laboratory by the glucose oxidation methodology using an oxygen electrode. Total cholesterol, LDL-C, HDL-C, and triglycerides were measured through the General Clinical Research Center Core laboratory using the Beckman Synchron CX9ALX system (Beckman Coulter, Fullerton, CA). For the remainder of the laboratory tests, serum was stored frozen at −80°C until sent for batch analysis. A commercial radioimmunoassay was used to measure insulin levels (Linco Research, Inc, St Charles, MO) for both studies (intra-assay coefficient of variation [CV], 3.1%; inter-assay CV, 6.0%; detection limit, 2 μU/mL; sensitivity, 100%). Insulin resistance was estimated, using fasting glucose and insulin levels, with the homeostasis model assessment (HOMA-IR) as described by Matthews et al.[27] In the ALLIFE study, C-reactive protein (CRP) measurements were performed based on a latex-enhanced turbidimetric immunoassay, which uses CRP Ultra Wide Range Reagent manufactured by Equal Diagnostics (Exton, PA) and Aeroset Chemistry Analyzer manufactured by Abbott Diagnostics (Irving, TX). In DHS, CRP measurements were performed using the Roche/Hitachi 912 system, Tina-quant assay (Roche Diagnostics, Indianapolis, IN).

Categoric CVD risk factors. Risk factor burden was estimated by a clustering of six CVD risk factors. Four of the risk factors used by the National Cholesterol Education Program Adult Treatment Panel III revised criteria for metabolic syndrome[28] were included: increased waist circumference (women, ≥ 88 cm; men, ≥ 102 cm); high triglyceride level (≥ 150 mg/dL or on a medication for hypertriglyceridemia); low HDL-C (women, < 50 mg/dL; men, < 40 mg/dL); and elevated blood pressure (BP; systolic BP ≥ 130 mmHg, diastolic BP ≥ 85 mmHg, or on a medication for hypertension). Recognizing the relatively young age of our cohort, we were particularly interested in those who had not yet developed hyperglycemia and were compensating by increasing their insulin production. Thus we used HOMA-IR

Table 1. Demographic Characteristics of ALLIFE and DHS Participants

Characteristic	ALLIFE (%; N = 118)	DHS (%; N = 782)	*P*
Age at study, years			< .001
18-24	63.6	0.0	
25-34	33.1	61.4	
35-37	3.4	38.6	
Sex			.11
Female	55.9	47.2	
Male	44.1	52.8	
Race and ethnicity			< .001
White, Non-Hispanic	72.9	41.8	
Black, Non-Hispanic	11.0	19.6	
Hispanic or Latino	13.6	34.7	
Other	2.5	3.8	
Education			.01
HS graduate or less	32.8	45.9	
HS graduate plus some college*	67.2	54.1	
Cancer therapy			
Chemotherapy			
Anthracycline	72.0	NA	
Cyclophosphamide	42.4	NA	
Dexamethasone	11.0	NA	
CRT			
Any CRT	33.9	NA	
< 24 Gy	9.3	NA	
≥ 24 Gy	24.6	NA	

Abbreviations: DHS, Dallas Heart Study; HS, high school; NA, not applicable; CRT, cranial radiotherapy.
*High school graduate plus some college or vocational training.

Table 2. Anthropometric Measures, Body Fat, and Metabolic Variables in Adult Survivors of Childhood ALL and Participants in the Dallas Heart Study

	DHS		ALLIFE					
			Cranial Radiotherapy			No Cranial Radiotherapy		
Variable	Mean	95% CI	Mean	95% CI	P^*	Mean	95% CI	P^*
Female survivors/participants								
Age, years	34.0	33.6 to 34.3	25.4	22.9 to 27.8	< .001	23.2	22.0 to 24.5	< .001
Height, cm	160.6	159.4 to 161.8	155.0	152.0 to 158.1	< .001	162.9	161.2 to 164.6	.58
Weight, kg	76.0	73.4 to 78.7	76.4	66.9 to 85.9	.78	73.5	67.2 to 79.8	.50
BMI, kg/m^2	29.5	28.5 to 30.5	31.6	28.1 to 35.1	.09	27.8	25.2 to 30.3	.41
Waist circumference, cm	90.7	88.6 to 92.8	96.4	89.7 to 103.2	.03	90.1	85.0 to 95.1	.80
Waist-to-height ratio	0.57	0.55 to 0.58	0.62	0.58 to 0.66	.001	0.55	0.52 to 0.59	.93
DXA								
Total fat mass, kg	27.9	26.4 to 29.4	32.5	27.0 to 38.1	.07	26.0	21.8 to 30.2	.47
Total body fat, %	36.5	35.4 to 37.6	42.4	40.4 to 44.5	< .001	35.1	32.5 to 37.7	.57
Metabolic variables								
Glucose, mg/dL	90.7	88.1 to 93.1	90.9	87.9 to 94.0	.12	87.4	85.3 to 89.6	.44
Insulin, μU/mL	11.1	10.0 to 12.2	20.5	16.5 to 25.3	< .001	15.3	13.2 to 17.7	< .001
HOMA-IR	2.4	2.2 to 2.7	4.6	3.6 to 5.7	< .001	3.3	2.8 to 3.8	< .001
Triglycerides, mg/dL	83.6	75.3 to 92.7	88.4	67.5 to 115.7	.59	68.4	57.5 to 81.5	.09
HDL-C, mg/dL	51.3	49.5 to 53.0	45.6	41.5 to 49.8	.008	47.9	44.4 to 51.4	.09
TG/HDL-C	1.7	1.5 to 1.9	2.0	1.4 to 2.7	.25	1.5	1.2 to 1.8	.34
Non-HDL	127.4	121.6 to 133.2	131.6	119.1 to 144.1	.48	114.0	105.3 to 122.8	.02
Non-HDL: HDL-C	2.7	2.5 to 2.9	3.0	2.6 to 3.5	.11	2.5	2.2 to 2.8	.42
LDL-C	106.1	102.0 to 110.2	110.9	97.1 to 124.8	.45	98.0	90.8 to 105.2	.07
CRP, mg/L	2.4	2.0 to 2.8	4.0	2.6 to 6.1	.03	1.5	1.0 to 2.3	.05
CRP per kg fat mass	0.09	0.08 to 0.10	0.13	0.09 to 0.19	.07	0.06	0.04 to 0.09	.04
Systolic blood pressure	112.9	111.4 to 114.5	107.9	102.9 to 112.8	.06	110.4	106.9 to 114.0	.14
Diastolic blood pressure	72.5	71.3 to 73.7	70.8	67.0 to 74.7	.35	71.3	68.6 to 74.1	.33
Male survivors/participants								
Age, years	33.5	33.1 to 33.9	27.1	24.3 to 30.3	< .001	22.0	20.8 to 23.2	< .001
Height, cm	173.3	171.9 to 174.6	171.6	166.8 to 176.3	.04	175.5	173.3 to 177.8	.58
Weight, kg	87.9	85.4 to 90.4	81.9	69.7 to 94.2	.16	80.8	75.7 to 85.9	< .001
BMI, kg/m^2	29.2	28.6 to 29.8	27.8	2.37 to 32.0	.51	26.2	24.7 to 27.7	< .001
Waist circumference, cm	98.7	96.9 to 100.4	94.6	85.6 to 103.6	.24	89.2	85.2 to 93.2	< .001
Waist-to-height ratio	0.57	0.56 to 0.58	0.55	0.50 to 0.61	.55	0.51	0.49 to 0.53	< .001
DXA								
Total fat mass, kg	21.3	20.4 to 22.2	23.9	17.6 to 30.2	.60	18.0	14.7 to 21.3	.01
Total body fat, %	24.6	23.8 to 25.3	28.5	25.0 to 31.9	.06	21.7	18.8 to 24.6	.03
Metabolic variables								
Glucose, mg/dL	91.7	90.0 to 93.3	94.3	90.0 to 98.7	.11	91.5	89.0 to 93.9	.64
Insulin, μU/mL	10.4	9.3 to 11.6	17.2	12.5 to 23.7	.004	15.0	13.1 to 17.1	< .001
HOMA-IR	2.3	2.1 to 2.6	4.0	2.8 to 5.6	.003	3.4	2.9 to 3.9	< .001
Triglycerides, mg/dL	117.2	105.4 to 130.3	99.1	64.8 to 151.5	.28	78.8	65.0 to 95.4	< .001
HDL-C, mg/dL	44.1	42.6 to 45.5	39.0	33.9 to 44.2	.17	41.2	37.9 to 44.4	.23
TG/HDL-C	2.7	2.4 to 3.1	2.6	1.6 to 4.4	.62	2.0	1.6 to 2.5	.001
Non-HDL	153.2	146.5 to 159.9	144.0	127.0 to 161.1	.11	132.8	121.9 to 143.7	< .001
Non-HDL: HDL-C	3.7	3.5 to 3.9	4.0	3.1 to 4.8	.73	3.4	3.0 to 3.8	.05
LDL-C	125.8	119.7 to 131.8	118.5	104.2 to 132.8	.17	115.1	105.5 to 124.7	.01
CRP, mg/L	1.6	1.4 to 1.9	2.4	1.4 to 4.1	.18	1.1	0.7 to 1.7	.09
CRP per kg fat mass	0.08	0.07 to 0.09	0.11	0.06 to 0.20	.21	0.07	0.05 to 0.10	.73
Systolic blood pressure	122.3	120.7 to 124.0	112.9	106.5 to 119.3	< .001	117.4	114.2 to 120.6	< .001
Diastolic blood pressure	75.7	74.4 to 76.9	70.7	66.1 to 75.4	.004	70.4	67.7 to 73.0	< .001

NOTE. The Dallas Heart Study population included 440 female and 342 male participants; the ALLIFE population included 66 female participants (CRT, n = 25; no CRT, n = 41) and 52 male participants (CRT, n = 15; no CRT, n = 37). Geometric means are reported for insulin, HOMA-IR, triglycerides, TG/HDL, and CRP. Sampling weights are incorporated for DHS estimates. For affected variables, data was omitted if individual was on a medication for hypertension, diabetes mellitus, or dyslipidemia.

Abbreviations: DHS, Dallas Heart Study; BMI, body mass index; DXA, dual energy x-ray absorptiometry; HOMA-IR, homeostasis model for insulin resistance; Non-HDL, total cholesterol −HDL; TG, triglycerides; CRP, C-reactive protein.

*P values are adjusted for race and ethnicity.

more than 2.86 (above the 75th percentile for HOMA-IR derived from the Third National Health and Nutrition Examination Survey)[29] rather than fasting glucose. In addition, with the evidence showing an independent and additive cardiovascular risk associated with an elevated CRP ($\geq$ 3 mg/L), this outcome was also included.

Statistical Analysis

Statistical analysis was performed with SAS version 9.1.3 (SAS Institute Inc, Cary, NC), using the SURVEYFREQ, SURVEYMEANS, SURVEYREG, and SURVEYLOGISTIC procedures to incorporate the complex sample design and race/ethnicity sampling weights for the DHS. In previous studies,

differences in the prevalence of obesity and other CVD risk factors have been found between men and women and between those treated with and without CRT.[8,9,11,13] Thus all comparisons were stratified by sex and CRT (yes/no). Variables with skewed distributions (insulin, HOMA-IR, triglycerides, triglycerides/HDL, and CRP) were log-transformed before analysis and are presented as geometric means. Comparisons of means and geometric means between ALLIFE versus DHS participants for anthropometric measures, body fat, and metabolic variables were adjusted for race and ethnicity. Odds ratios (OR) and 95% CIs for multiple CVD risk factors in the ALLIFE group relative to DHS were determined using logistic regression analysis and a two-sided significance level of .05.

RESULTS

Characteristics of ALLIFE and DHS Participants

Table 1 provides demographic characteristics of the ALLIFE and DHS participants, in addition to some key treatment characteristics of the ALLIFE group. Among women, the mean ages of ALLIFE CRT and no CRT participants were 25.4 and 23.2 years, respectively (Table 2). Women in DHS, with a mean age of 34.0 years, were older than participants of both these groups. Similarly, men in DHS, with a mean age of 33.5 years, were older than ALLIFE men (CRT, 27.1 years; no CRT, 22.0 years; Table 2).

Individual Cardiovascular Risk Factors

Obesity-related outcomes. Although BMI was not significantly different between female ALL survivors who had been treated with CRT (31.6; 95% CI, 28.1 to 35.1) and women in DHS (29.5; 95% CI, 28.5 to 30.5), the ALLIFE CRT women had a greater waist circumference, higher waist-to-height ratio, and higher percent total body fat (Table 2). The obesity-related measures were not different between the ALLIFE no CRT women and the DHS women, who were an average of 10.8 years older.

The BMI, waist circumference, and waist-to-height ratio were not different between ALLIFE CRT men and DHS men (Table 2). Percent total body fat was nonsignificantly increased ($P = .06$) in ALLIFE CRT men (28.5%) versus DHS men (24.6%). The ALLIFE no CRT men had a lower BMI, smaller waist circumference, lower waist-to-height ratio, and lower percent total body fat than the DHS men.

Glucose, Insulin, and HOMA-IR

Fasting glucose levels were not different between ALLIFE women (with or without CRT) and DHS women (Table 2). However, fasting insulin levels were higher ($P < .001$) in both ALLIFE CRT women (mean, 20.5 μU/mL; 95% CI, 16.5 to 25.3 μU/mL) and ALLIFE no CRT women (mean, 15.3 μU/mL; 95% CI, 13.2 to 17.7 μU/mL) in comparison with women in DHS (mean, 11.1 μU/mL; 95% CI, 10.0 to 12.2 μU/mL). Similarly, the HOMA-IR was elevated ($P < .001$) in both ALLIFE CRT women (mean, 4.6; 95% CI, 3.6 to 5.7) and ALLIFE no CRT women (mean, 3.3; 95% CI, 2.8 to 3.8) in comparison with DHS women (mean, 2.4; 95% CI, 2.2 to 2.7). When further adjusted for BMI, these differences remained significant ($P < .001$) between both ALLIFE groups compared with DHS women. Figure 1 displays a scatterplot of the HOMA-IR by group.

These findings were similar, though attenuated, among the men (Table 2). Although fasting glucose levels were not different across groups, ALLIFE CRT and no CRT men had higher ($P < .005$) fasting insulin levels in comparison with DHS men. Similarly, the HOMA-IR was elevated ($P < .005$) in both ALLIFE CRT men (mean, 4.0; 95% CI, 2.8 to 5.6) and ALLIFE no CRT men (mean, 3.4; 95% CI, 2.9 to 3.9) in comparison with DHS men (mean, 2.3; 95% CI, 2.1 to 2.6). Again, adjusted for BMI, these differences remained significant ($P < .001$) between both ALLIFE groups and DHS men.

Lipids

With the exception of a lower HDL, ALLIFE CRT women had cholesterol levels that were similar to DHS women (Table 2). In contrast, ALLIFE no CRT women had lower levels of triglycerides and non-HDL than DHS women. ALLIFE CRT men had lipid levels similar to those of DHS men, whereas ALLIFE no CRT men generally had lower levels of triglycerides, LDL-C, and non-HDL (Table 2).

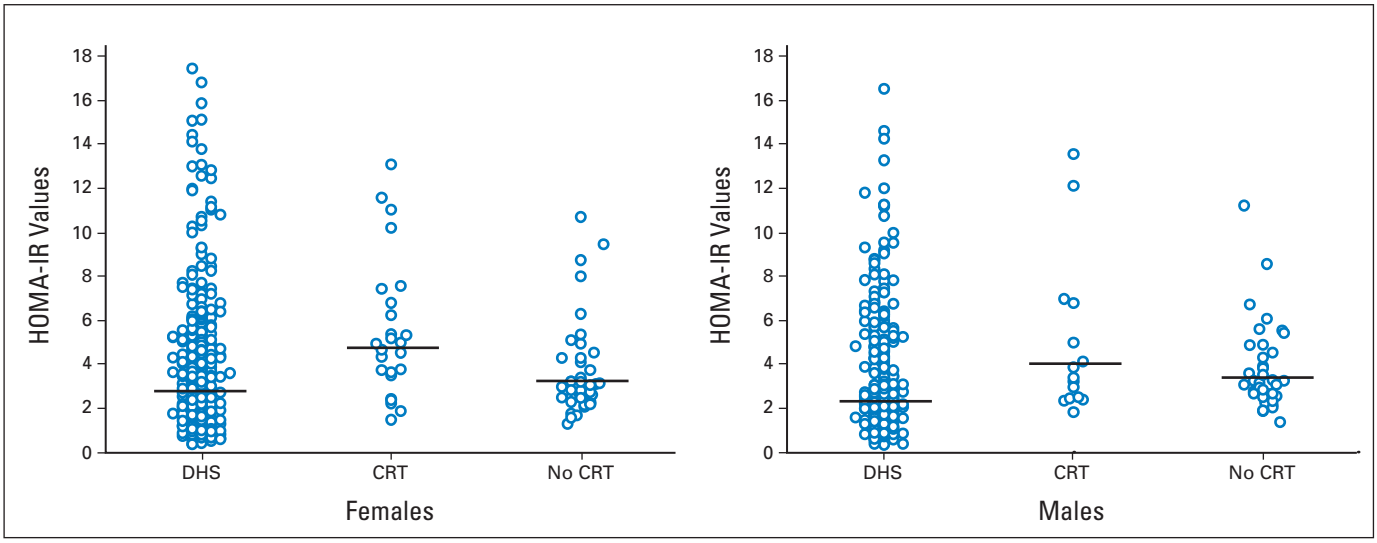

Fig 1. Scatterplot with geometric mean homeostasis model for assessment of insulin resistance (HOMA-IR) by group and sex. DHS, Dallas Heart Study; CRT, patients in the ALLIFE study who underwent cranial radiotherapy; no CRT, patients in the ALLIFE study who did not undergo CRT.

CRP

ALLIFE CRT women had a higher CRP (mean, 4.0; 95% CI, 2.6 to 6.1) in comparison with DHS women (mean, 2.4; 95% CI, 2.0 to 2.8). The CRP in ALLIFE no CRT women (mean, 1.5; 95% CI, 1.0 to 2.3) was lower than that of DHS women (Table 2). Among men, the CRP levels were similar among ALLIFE and DHS participants (Table 2).

Blood Pressure

The systolic blood pressure was not different for ALLIFE women in comparison to DHS women. In contrast, ALLIFE men with and without CRT had lower systolic and diastolic blood pressure in comparison with DHS men.

Clustering of CVD Risk Factors

Eighty percent of ALLIFE CRT women had three or more of six CVD risk factors, which was higher than women in DHS (40.1%; Table 3). When compared with DHS women, ALLIFE CRT women were 5.96 (95% CI, 2.15 to 16.47) times as likely to have three or more risk factors (Table 4). ALLIFE no CRT women, with 41.5% having three or more risk factors, were not different from DHS women. Among males, the prevalence of having three or more CVD risk factors was not different between ALLIFE CRT (33.3%) and no CRT men (27.0%) in comparison with DHS men (33.9%).

Table 3. Prevalence of Categorical CVD Risk Factors, by Sex, in Adult Survivors of Childhood ALL and Participants in the Dallas Heart Study

		ALLIFE			
		Cranial Radiotherapy		No Cranial Radiotherapy	
CVD Risk Factor	DHS (%)	%	*P*	%	*P*
Women					
Individual risk factors					
HOMA-IR ≥ 2.86*	43.9	80.0	.001	56.1	.16
Triglycerides ≥ 150 mg/dL	15.7	24.0	.36	7.3	.09
HDL-C < 50 mg/dL	47.9	72.0	.03	63.4	.07
BP ≥ 130/85	15.5	8.0	.22	7.3	.10
Waist ≥ 88 cm	49.8	64.0	.18	48.8	.90
CRP ≥ 3.0 mg/L	43.6	64.0	.06	36.6	.40
No. of risk factors					
0	21.0	12.0		12.2	
1-2	38.9	8.0		46.3	
3-4	30.2	64.0		34.1	
5-6	9.9	16.0		7.3	
≥ 3	40.1	80.0	< .001	41.5	.87
Men					
Individual risk factors					
HOMA-IR > 2.86*	34.7	66.7	.04	59.5	.01
Triglycerides ≥ 150 mg/dL	35.9	33.3	.84	13.5	.004
HDL-C < 40 mg/dL	39.7	53.3	.33	43.2	.70
BP ≥ 130/85	22.5	6.7	.05	8.1	.01
Waist ≥ 102 cm	33.8	26.7	.56	16.2	.03
CRP ≥ 3.0 mg/L	25.8	33.3	.56	21.6	.58
No. of risk factors					
0	23.0	13.3		21.6	
1-2	43.1	53.3		51.4	
3-4	27.7	26.7		24.3	
5-6	6.3	6.7		2.7	
≥ 3	33.9	33.3	.96	27.0	.40

Abbreviations: CVD, cardiovascular disease; DHS, Dallas Heart Study; HOMA-IR, homeostasis model for insulin resistance; BP, blood pressure; CRP, C-reactive protein.

*Abnormal HOMA-IR values were defined as more than 2.86, which was the 75th percentile for HOMA-IR derived from participants in the Third National Health and Nutrition Examination Survey.[29]

DISCUSSION

We report that young adult survivors of childhood ALL, regardless of sex or treatment with CRT, were significantly more likely to have insulin resistance compared with a representative cohort of individuals from the same community but, on average, 10 years older. In particular, women treated with CRT, in comparison with older women in the DHS, were more likely to be insulin resistant, have decreased HDL levels, and have elevated CRP levels. In fact, women treated with CRT were six times more likely to have three or more CVD risk factors as the DHS women.

Among ALL patients undergoing therapy, alterations in glucose metabolism are common.[30] Mohn et al[31] reported an impaired insulin response in patients who had been off therapy for 1 year, but over time, this impairment resolved.[32] However, recent studies suggest that some childhood ALL survivors, depending on therapy, may have a persistent risk of insulin resistance in their young adult years.[11,13,33] In a comparison of 44 ALL survivors who had been treated with CRT (median age, 24.8 years) with 44 age- and sex-matched controls, Link et al[13] reported that the survivors had significantly higher fasting insulin and glucose levels. Further, survivors had significantly higher BMI, increased waist circumference, and higher waist-to-height ratio. Gurney et al[11] reported that fasting insulin levels and HOMA-IR were significantly higher in 50 young adult survivors of childhood ALL treated with CRT compared with 25 survivors treated with only chemotherapy. Neither of these two studies reported outcomes by sex.[11,13] Our study is the first that we are aware of that shows an increased prevalence of insulin resistance in young adult survivors of childhood ALL for both those treated with and without CRT and for both sexes. Importantly, this finding remained significant for each group after adjusting for BMI.

It is now apparent that CRP independently predicts cardiovascular disease, particularly among women.[34-37] An elevated CRP level

Table 4. Odd Ratios With 95% CI of Having Multiple CVD Risk Factors, by Sex, in Adult Survivors of Childhood ALL (ages 18 to 37 years) Compared With Participants in the Dallas Heart Study (ages 30 to 37 years)

	Cardiovascular Risk Factors			
	≥ 2 Risk Factors		≥ 3 Risk Factors	
Group	OR	95% CI	OR	95% CI
Women				
DHS (reference)	1.00		1.00	
ALLIFE CRT	3.42	1.14 to 10.53	5.96	2.15 to 16.47
ALLIFE no CRT	1.42	0.69 to 2.93	1.06	0.54 to 2.09
Men				
DHS (reference)	1.00		1.00	
ALLIFE CRT	1.61	0.52 to 5.01	0.97	0.32 to 3.00
ALLIFE no CRT	0.61	0.29 to 1.29	0.72	0.32 to 1.60

Abbreviations: CVD, cardiovascular disease; ALL, acute lymphoblastic leukemia; OR, odds ratio; DHS, Dallas Heart Study; CRT, cranial radiotherapy.

among women in the general population is associated with insulin resistance and metabolic syndrome.[36] Notably, a CRP of 3 mg/L or higher in women has an additive effect when combined with metabolic syndrome in predicting future cardiovascular events.[35] Nearly two thirds of the women in our study treated with CRT had a CRP of 3 mg/L or higher. Although one might expect elevated CRP levels in this more obese group of women,[25,38,39] the CRP per kilogram fat mass among women treated with CRT was nonsignificantly higher than the women in DHS ($P = .07$), suggesting that there may be another mechanism leading to this increased CRP.

Much attention has been directed to the predictive value of the metabolic syndrome.[28,40-42] Individuals with multiple CVD risk factors have a more than additive risk of cardiovascular disease. Recognizing the relatively young age of our cohort, we were interested in those who had not yet developed hyperglycemia and were compensating by increasing their insulin production and thus used HOMA-IR rather than fasting glucose. Also, recognizing the above studies showing the independent and additive risk associated with an elevated CRP, this outcome was included. Notably, women treated with CRT were six times as likely to have three or more CVD risk factors as women living in the same community who were 10 years older. This increased prevalence of CVD risk factors among women treated with CRT is likely secondary to several interrelated factors, including obesity,[7,8] growth hormone deficiency or insufficiency,[11,13] leptin insensitivity,[43,44] and physical inactivity.[9,10] Interestingly, studies continue to suggest that women are more adversely affected by CRT than men.[8,9,16,44,45] Adult women treated for childhood ALL with CRT have a much greater rate of increasing BMI than men treated with the same therapy.[7]

Several limitations of the study should be appreciated when interpreting the findings. This data is cross-sectional and limits the analysis to assessing strengths of association. The sampling approach used for ALLIFE (based on cancer registry) is different from that used for DHS (probability-based county sample). To balance the differences of race and ethnicity, DHS sampling weights were used to provide estimates representative of the Dallas area. Further, comparisons between ALLIFE and DHS participants were adjusted for race and ethnicity. DHS participants were significantly older than ALLIFE participants, with increasing age being strongly associated with each of the outcome measures.[19-21,46,47] Thus this study may underestimate the burden of cardiovascular risk factors among ALL survivors. The gold standard of measuring insulin resistance is the expensive and labor-intensive euglycemic-hyperinsulinemic clamp.[48,49] Although in children there seems to be only a modest correlation between HOMA-IR and clamp measures of insulin sensitivity,[50] there is good correlation between these two tests among adults.[49,51-55] For this reason, HOMA-IR is a widely used and inexpensive tool to estimate insulin resistance.[49,54,55] Lastly, different DXA methods were used for the two studies. However, the mean difference between measured body weight and total mass weight estimated by DXA was similar (ALLIFE = −1.5, 95% CI, −1.8 to −1.2; DHS = −1.4, 95% CI, −1.5 to −1.2). The bias is similar for the two groups with respect to magnitude and direction, suggesting that there is likely not a clinically significant inconsistency introduced by the use of these two DXA methods.

In summary, ALL survivors, regardless of sex and therapy, have an increased prevalence of insulin resistance. Further, women treated with CRT have a substantially increased prevalence of various CVD risk factors. Close monitoring and interventions aimed at reducing cardiovascular risk in survivors of childhood ALL are warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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